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The invention concerns a continuous procedure for the production of morphologically uniform micro and nano-particles by means of micro mixer, the encapsulation of active substances with this procedure, as well as in this procedure manufactured particle.

The registration are the basis the following definitions;
Nano-particle: Particle with a particle size of 1-1000 Nm:
Micro particle: Particle with a particle size of 1 mu m -1000 mu M. Particle: Micro or nano-particle independently of the distribution of the particle-forming substance in the particle.
Caps: special form of a particle, by the fact characterized that the particle screen and substance is present as wrapping screen end cap wall.
Particle screen and substance: Wandbildner and/or. Imbedding material of particles or pure active substance.
Koazervation: Transfer of a solved polymer into a polymere-rich, phase still containing solvent by means of Desolvatation. The simple Koazervation can be caused by salting out, change of temperature, change of pH or solvent additive. With a complex Koazervation the Desolvatation is released by ions or polymers loaded opposite.
Microencapsulation: Encapsulation of an active substance in a particle.
Solvent withdrawal: Distance of organic solvents by evaporation and/or extraction.
Internal phase: I, disperse, dispersed phase.
Expresses phase: A, dispersing agent.
Natural substances: Substances of natural origin, as well as nature-identical and nature-similar substances.
Micro mixer: Mixer, in which at least two fluids media at at least one boundary surface are brought to m in the form of liquid lamellas smaller 1000 mu intimately in contact.
Static mixer: continuously operable mixers without mobile installations.
The well-known procedures for the production of micro or nano-particles can be divided as follows:

1. Phasentrennverfahren-Koazervation

- simply
- complex

2. mechanical-physical procedures

- Spraying procedures
- Centrifugal procedures
- Hot emulsion procedures

▲ top

3. Polymerization procedure

- Emulsion polymerization (polymerization within disperser phase)
- Interface polymerization (polymerization at boundary surface disperse phase/dispersing agent)

4. Procedure over polymer dispersions

- Heat denaturing
- Desolvatation
- Solvent evaporation (solvent evaporation)

All procedures are operated intermittent and are suitable for the microencapsulation of active substances into a biodegradable synthetic polymer matrix and/or. Copolymer matrix and/or into natural substances.

From the literature well-known synthetic polymers for this purpose are PP, Polyanhydride, polyester, Polyorthoester, Polyacetate, Polylactone, Polyorthocarbonate and. A.. Above all so far Polylactid and Polylactid coglycolid polymers application found.

As natural substances for microencapsulation for example fats and proteins are suitable such as gel and albumin, as well as Polysaccharide and their derivatives such as z. B. Strength and cellulose and their derivatives, Alginate and Chitosan.

Like that are z. B. from US 4.675.189 (Syntex Inc.), US 4.835.139 (Debiopharm S.A.) and EP 302,582 B1 (Southern Research Inst.) pharmaceutical compositions of water-soluble Peptide and proteins admits, which were manufactured on the basis of the Koazervation.

The disadvantages of this procedure consist apart from the use of toxicological problematic means such as Dichlormethan, heptane and silicone oil also of the fact that the different process steps which can be accomplished permit only an intermittent enterprise.

A procedure for the production of biodegradable micro particles of water-soluble Peptiden and proteins, described in EP-A 315875 (most AG), is based on the spray drying procedure, with which an aqueous peptid or protein solution in an organic polymer solution emulsified and this emulsion becomes spray-dried. Also this procedure is only intermittent feasible.

After the ?solvent - evaporation - procedures? manufactured micro particles are in two Canadian patent applications APPROX. 2.100.925 (Rhone Merieux) and APPROX. 2.099.941 (Tanabe Seiyaku of cost.) described.

Usually with this method the active substance is loosened, suspended in an organic polymer solution or directly and/or. as aqueous solution emulsifies. After addition these polymer/the polymer solvent one evaporates to active substance dispersion to a second aqueous phase with an boundary surface-active substance.

This method is very variable and it O/W, in addition, W/O or complex W/O/W emulsions is normally manufactured (Mueller/Hildebrand: Pharmaceutical technology: Modern medicine forms, Wiss. Publishing house company, 2. Aufl., S. 243-258, 1998)

Essential disadvantage of these procedures is also here that it concerns intermittent procedures. In the laboratory yardstick production z takes place. B. in the beaker, when industrieller production remains the production way, since the beginning container is only increased.

Manufacture parameter such as z. B. the dispersion time are not directly transferable from the laboratory to the technical school yardstick. These differences lead to difficulties with the Scaling UP. Due to a large mixing capacity strongly differently mixed ranges develop with large mixers during dispersion in the medium. Dispersion is inhomogenous and it results non-uniform products.

In the EP 0167825 dispersion becomes z. B. with high-speed mixers such as rotor stator systems described. It is unfavorable that without uniformity distributed power densities in the dispersion medium arise and the particles thereby become non-uniform.

The US patent specification 5.108.837 describes for example dispersion by acoustic irradiation by means of ultrasonic staffs. The products are however often contaminated with metal (z. B. with titanium of the ultrasonic staff). Additionally the power density is inhomogenous both around the agitator and around the head of the ultrasonic staff, which leads to Polydispersität of the particles (Weyhers, H, thesis writing, free University of Berlin, 1995).

A further possibility exists in dispersion by means of Hochdrucknomogenisation. Usually uniform particles can be manufactured, but the erosion at the cavitation gap, arising under high pressures, contaminates the product with metal ions. Additionally the temperature points arising with Hochdruckhomogenisatoren can decompose sensitive active substances. The high shear load due to the high pressure (100-2000 bar) knows the decomposition of
▲ top macromolecules (z. B. Albumin) to the consequence have.

An improvement of the W/O/W technology becomes in the patent application WO97/19676 (24.11.95) stressed, as with the dispersion process an additional phase inversion process is induced. A W/O emulsion is manufactured by agitating, whereby the water phase contains the active substance. With further additive of active substance-free water phase a phase inversion takes place to the W/O/W system, which is conventionally processed under agitating. Since still two dispersion processes are involved, the problems described above remain existing. In addition it comes however still that the phase inversion process must be additionally still controlled.

Further procedures are described, with which the particle matrix in liquid form in an outside not mixable phase is distributed directly. Examples are the production of firm Lipidnanopartikel by rotor stator of systems, by Ultrabeschallung or by Homogenisation (EP 0605497; Siekmann et al. Pharm. Pharmacol. Lett., 1 (1992) 123-126).

Further medicine forms are described, in which the particle screen and substance is pure active substance. The production of particles from pure active substances can take place also via Hochdruckhomogenisation (German patent application No. 4440337.2). The disadvantages described above generally apply. A further manufacture possibility exists in grinding the particles (z. B. by Perl mills as with NanoCrystals). The product is however loaded by the abrasion of the meal balls (book man et al., 42< ip> Congress APV, 124, Mainz, Germany 1996).

A beginning for the continuous production of micro particles is the use of a commercial rotor stator flow cell such as z. B. of Janke and Kunkel (Ika laboratory technology, Staufen, Germany) or Silverson (Silverson Machined Limited, Chesham, United Kingdom). The latter becomes z. B. in the PCT registration WHERE 98135654 described. The rotor of stator problems discussed above remains. Particularly for aseptische production additionally problems result concerning. Sterility, since the seals necessary with these rotors are susceptible to germ trimming.

The difficulty of the realization of a suitable industrial procedure for the production of nano-particles is proven also by the fact that so far despite more than 30 years the medicine form nano-particle on the market does not exist to intensive research. Apart from technical problems (realization of a continuous process, costs of the process) still the often which is missing qualification ability of the plants is added.

In summary the following disadvantages of the state of the art result:

1. Intermittent production engineering
2. Differences in production conditions of laboratory and technical school yardstick, thereby difficulties the Scaling UP
3. inhomogenous mixing conditions in the large beginning
4. non-uniform products
5. Controllableness of the process
6. Product load by production process (contamination)
7. Active substance decomposition
8. Costs of the process
9. Validating ability and qualification of the process and/or. the plant.

Task of the invention is it, a continuous procedure for the production morphologically more uniformly, not too received to agglomerierender micro and nano-particle without use of organic solvents or using toxicological harmless solvents, which are suitable for the microencapsulation of active substances and which permit a problem-free transfer of a laboratory on a production yardstick (?Scaling UP?). Further the manufacture conditions should not entail product load and active substance decomposition.

The task of the invention becomes surprisingly simple by means of a micro mixer (fig. 1 to 4) solved. According to invention used the micro mixers are based thereby on a simple, but versatile multi-laminated principle. The liquids are pressed by a lamella layer, whereby the layer thickness of the withdrawing liquid is in the micrometer range.

The central element of such a micro mixer is a mixing chamber with an interlinking micro-channel arrangement. The walls of the micro-channels can be differently formed out. For example the walls straight can, zigzag or wavy its (fig. 5). The mixing chamber can be made for example by means of a combination of lithography, Galvanoformung and casting (LEAGUE). The micro-channel width is variable and lies between 1-1000 mu m, preferentially between 1 and 500 mu m and particularly preferentially between 2 and 100 mu M.

The liquids which can be mixed become pressure-free or with liquid pressures up to approx. 30 bar over inlet drillings the multi-duct system supplied. This can in the z. B. in the Gegenfluss, equal river or also coaxially take place. It comes to the periodic lap of the liquid lamellas. The mixing product is taken off thereby not over the entire surface of the mixing chamber, but perpendicularly or parallel to the river direction over a discharge opening channel, which forces the complete penetration within a defined contact zone.

With this micro mixers surprisingly continuously micro particle can be manufactured. Additionally the particles won with the procedure are characterised surprisingly by a uniform particle size.

In the available invention the mixing area of the yardstick of several 100 litres by the use of micro mixers (z becomes. B. Beco mixing mixer) on a volume maximally few cm< 3>, usually under 1 cm< 3>, with a surface area of usually less than 3 cm< 2> reduces. It results a low power density and the product load is minimized.

▲ top With usual liquid pressures of 1-2 bar flow volumes can be achieved of 1-1,5 L per hour. Pressures can do in addition, up to approx. 30 bar for pumping the liquids by the columns of the mixer to be used, with suitable construction of the mixers also higher pressures. Thus the flow volumes can be increased accordingly that is called per hour can with a mixer far more than 10 L product are produced.

By variation the micro-channel width and the discharge opening channel width can be adapted the mixing unit on many different manufacture parameters such as river rate, pressure and liquid characteristics such as viscosity. Thus know particle size and - distribution of the manufactured micro particles to be within wide limits affected and controlled.

Advantage of the invention is that a Scaling UP without change of the manufacture conditions can take place, i.e. the product quality remains unchanged. By a parallel use of micro mixers the flow rate and thus the throughput can in a simple manner be increased. Alternatively also several vorgefertige mixer arrays can (consisting of z. B. 10 single mixers) to be used. A Scaling UP of the laboratory on a production yardstick can be reached thus simply by the increase of the number of micro mixers (numbering UP).

The supply of the phases comes in each case from a common storage vessel for all mixers. The diameters of the supply lines are so regulated that with each mixer identical pressure ratios and flow rates prevail. Even in the case of a low pressure of 1-2 bar arise in a mixer array approx. A throughput of 50 L particle dispersion per hour already in-stands for 5 L product per hour, i.e. with combination of only 10 arrays.

The invention is suitable outstanding for the aseptischen production of particles. Micro mixers made of metal can be used (z. B. Steel, silver), which can be autoklaviert and sterilized even with heat. The supplied phases can be problem-free sterile filtered. Even with melted Lipiden sterile filtration under pressure is problem-free possible. With aseptischen production the feed pumps are switched before the sterile filters. Production in the mixer takes place

then under aseptischen conditions in the laminar air flow. Particularly the use of silver micro mixers is here recommendable, there additionally still the oligodynamische effect (cunning: Medicine form teachings, Wiss. Publishing house company, 3. Aufl., S. 445, 1982) to carrying comes.

There is switch-selectable most at present still intermittent operated procedures also with a micro mixer on the continuous enterprise.

The micro particle formation can occur with it directly in the contact zone or temporally retarded. The micro and/or. Nano-particle suspension is taken off over the discharge opening and can be regenerated if necessary further.

The encapsulation of an active substance can take place depending upon its solubility in simple way. The active substance is loosened simply, directly or solved in a suitable medium, in the particle-forming liquid phase, suspended or emulsified.

If it is necessary to emulsify the active substance or an active substance solution this can be appropriately managed in an upstream mixer, preferably micro mixers or by an additional inlet drilling.

If the production of an organic solution of the particle-forming substance is not avoidable, it can become necessary, nachzuprozessieren the won micro particle dispersion. In the simplest case the remainder solvent leaves itself to CROSS flow by means of a filtration or a thin section evaporator (z. B. Sambay) in the continuous enterprise remove. Thin section evaporation and CROSS flow filtration are suitable besides for the distance of unverkaspeltem active substance and/or/the Tenside.

By way of the inlet drillings the particle screen end liquid phase and the dispersion medium are supplied to the micro mixer.

The particle screen end liquid phase can be:

1. the aqueous solution of a particle-forming substance (z. B. Gel solution, active substance solution)
2. an organic solution of a particle-forming substance (z. B. PLGA in ethyl acetate, active substance solution)
3. a melted (z. B. Fat, active substance, polymer) particle screen end substance

The particle-forming liquid phase can if necessary. Tenside, Viskositätserhöher or other stabilizers to be added.

The dispersion medium can be:

1. Water or an aqueous solution
2. a hydrophilic liquid (z. B. Glycerol)
3. an organic solution
4. oily liquid (z. B. mittelkettige Trigylceride, castor-oil, peanut oil)
5. In or multi-phase mixtures from the media 1 to 4
6. The Koazervation releasing or solubility-decreasing substances, Tenside and/or Viskositätserhöher can be added to the dispersing agent.

The micro particle or nano-particle formation takes place depending upon particle-forming liquid phase via
▲ top solidification, solidification via solvent withdrawal and/or Koazervation.

In the following the differently possible procedure variants are more near described:
Procedure variant I: To the production of polymer particles or particles from macromolecules the polymer or the macromolecule is loosened in an organic phase and is not then dispersed these as internal phase of one with their mixable outside phase by means of micro mixers. For the stabilization of the received dispersion the phases Tenside or other stabilizers can be added. The distance of the solvent is made via continuous evaporation by a thin section evaporator (z. B. Sambay) or by CROSS flow filtration. For solidification the particle can be void a separate distance of the solvent, if the solvent possesses a sufficiently high solubility in water. The particles can be separated in this case by conventional separation methods such as filtration, sedimentation or Zentrifugation.
Procedure variant II: Alternatively to the distance of a solvent the particles can be manufactured also by Koazervation. The Koazervation can take place via ions loaded opposite (z. B. by CaCl2 with Alginaten). One proceeds in this case in the way that in the micro mixer particle screen end is dispersed a phase of a koazervierbaren substance in a phase, which contains the Koazervation releasing substance. The Koazervation can also by physical measures like the increase of the temperature (z. B. Heat denaturing by proteins) to be released.
Procedure variant III: Particles can be manufactured also without solvents, if the particle matrix can be transferred by warming up into the liquid state of aggregation (z. B. at ambient temperature firm of Lipide, waxes or polymers). One proceeds in this case in the way that in the micro mixer a melted particle matrix in a suitable dispersion medium is dispersed at increased temperature. In the dispersion medium if necessary still Tenside can be solved.
Procedure variant IV: For the production of caps z can. B. liquid cap contents (oil or liquid Lipid) solved in the micro mixer in an outside phase to be dispersed, those the wall material contain (z. B. Gel in water). The manufactured dispersion is led directly into a precipitation solution (z. B. 5% NaCl solution). The wall material (z. B. Gel) precipitates and draws themselves up in the context of the phase separate ion process on cap contents.
Procedure variant V: For the production of caps after the W1/O/W2-Prinzip two micro mixers or a static mixer and a micro mixer are connected in series. In the first mixer the W1 phase in the organic solvent is dispersed, which contains the matrix material in solved form (z. B. PLA in ethyl acetate). In the mixer downstream the W1/O

emulsion in the aqueous phase W2 is then dispersed. Develops a W1/O/W2-System, which can be dried as under variant I.
Procedure variant VI: For the production of particles from pure active substance the active substance is melted and similarly to variant III proceeds
Procedure variant VII: For the production of particles from pure active substance the active substance can be loosened also in a solvent, which is supplied to the micro mixer as internal phase as well as a dispersing agent. The Präzipitation particles is reached by removing the solvent similar to variant I.
Procedure variant VIII: To the production of particles from koazervierbaren substances (z. B. Alginate) it can be proceeded also in such a way that the Koazervation releasing substance forms only during the production (z. B. Acetic acid from acetic anhydride by hydrolysis). This substance can release thereby directly the Koazervation themselves or induce the education of the koazervierbaren substance (z. B. Release of calcium ions from a complex).

As particle screen end substance biodegradable, synthetic and/or natural substances can be used. The particles can consist also of pure active substance. The particle screen end substance can be prefabricated or during the production z. B. from Koazervation result.

As biodegradable synthetic polymers are prefer polyesters of hydroxy acids, which can be used in the procedure according to invention:
Polyglycolide (PGA) and copolymers of Glycoliden such as Glycolid/Lactid
Copolymers (PGA/PLLA = PLGA) or Glycolid/Trimethylencarbonat
Copolymers (PGA/TMC); L-Polylactide (PLA) and Stereocopolymere of Polylactiden such as Poly L Lactid (PLLA), Poly DL Lactid of copolymers and L-Lactid /DL-Lactid copolymers; Copolymers of PLA such as Lactid/Tetramethyiglycolid
Copolymers, Lactid/delta - Valerolacton copolymer and Lactid/epsilon - Caprolacton
Copolymer; Poly beta - (PHBA), PHBA/beta - Hydroxyvalerat of copolymers (PHBA/HVA) hydroxybutyrat, Poly ßß hydroxypropionat (PHPA), Poly p dioxanon (Party of Democratic Socialism), Poly delta - hydrophobisierte valerolacton, Polysaccharide, - Hyaluronsäure, - Dextrane or hydrophobisiertes Amylopektin and Poly epsilon - caprolacton.

As block copolymers of polyesters of hydroxy acids and linear or star polyethylene glycol (PEG) those can find application in the following specified in the procedure according to invention:
Off block copolymers from PLA or PLGA and PEG, ABA Triblock copolymers from PLA PEG PLA and/or. - PLGA, S (3) - PEG-PLA and/or. - PLGA of block copolymers and S (4) - PEG-PLA and/or. - PLGA of block copolymers.

PLGA polymers with a Lactid/Glycolidverhältnis of 50 are preferential in accordance with the invention: 50, 75 : 25, 85 : 15 or between them lying mixtures. The used molecular weights are appropriate 1000 and 300000 Dalton between. Also mixtures of different molecular weights can be present. Molecular weights between 20000 and 200000 Dalton are preferential.
Examples of these preferential polymers are Resomer TM RG-505 in particular Resomer TM RG-756 or Resomer TM RG-858.

Preferential ones natural substances according to invention are fats (Lipide and Lipoide), natural and artificial mono, and Triglyceride, natural and artificial of waxes, hydrocarbons, Fettalkohole and their esters and Ether, Lipidpeptide, proteins and sugar derivatives or their mixtures such as z. B.:
Glycerintrilaurat, - myristat, - palmitat, - stearat, - behenat, Glycerintriolpat, Glycerolmonopalmitostearat, Cetylpalmitat, Kokosfett, Stearylalkohol, Glycol, Butandiol and Glycerolester of the following fatty acids:
Ant, vinegar, prop. Ion, butter, Valerian, Capron, Önanth, Capryl, Pelargon, Caprin, and CAN, Laurin, tri DEK en, Myristin, Pentadecan, palmitin, Margarin, stearin, Nonadecan, Arachin, Behen, Lignocerin, Cerotin, Melissin, ISO butter, Isovalerian, Tuberculostearin, acryl, Croton, Palmitolein, oil, Eruca, Sorbin, Linol, Linolen, Elaeostearin, Arachidon, Clupanodon and/or Docosahexaensäure, hard paraffin, Oleylalkohol, Stearylalkohol, Cetylalkohol, bleached wax, gel, human serum albumin, Bovinserumalbumin, Natriumalginat, Chitosan, cellulose, methyl cellulose, ethyl cellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Pektin, Xanthan and strength or their mixtures.

▲ top

Preferential according to invention halogeneous-free solvents or solvent mixtures are ethanol, isopropanol, methanol, alkyl acetates such as methyl, ethyl, Propyl, Isopropyl or butyl acetate, alkyl formates such as methyl, ethyl, Propyl, Isopropyl or Butylformiat, tri monacetin, tri ethyl CIT advice and/or C1-C4 Alkyllactate z. B. Methyl or Ethyllactat, Ketone z. B. Acetone, Ethylmethylketon.
Particularly to be preferred methyl acetate, ethyl acetate, Isopropylacetat and Propylformiat assigned.

In the sense of the invention as surface-active substances prefers substances from the Pofoxamere TM group, Polyethylenglycol Alkylether, Sorbitanfettsäureester (splinter ©&), ethoxylierte Sorbitanfettsäureester (Polysorbate, Tween ©&), Saccharoseester (Sisterna ©&, the Netherlands, Ryoto sugar ester, Tokyo), gel, Polyvinylpyrrolidon, Fettalkoholpolyglycosid, CHAPS, CHAPSO, Decyl beta - D-Glycopyranosid, Decyl beta - D-Maltopyranosid, Dodecyl beta - D-Maltopyranosid, sodium oleate, Poloxamine TM group, polyethylene glycol, Polyvinylalkohol, polyoxyethylierte Fettsäureether (Brij ©&), triton X-100, Lecithine or Lecithinderivate, Cholesterin and Cholesterinderivate, Cholate, Phospholipide or their mixtures.

Phospholipide, polyvinyl alcohol, Brij TM, Poloxamere TM, Poloxamine TM, Tween TM and Saccharoseester or their mixtures application find preferred.

Further the use of viscosity-increasing substances is possible for the stabilization of the internal and outside phase.

For example Celluloseether can do and - esters such as methyl cellulose, Hydroxyethylcellulose or

Hydroxypropylcellulose, Polyvinylderivate such as polyvinyl alcohol, Polyvinylpyrrolidon or Polyvinylacetat, Polyacrylsäure (z. B. Carbopol) and their derivatives as well as Xanthane or Pektine and their mixtures to be used.

The subject of the invention are also morphologically uniform micro and/or. Nano-particle particles, which are manufactured in the procedure mentioned. The particle size distributions are very close.

Subsequently, the invention with remark examples is more near described, without limiting it to it.

Example 1

Production of PLA Mikropartikeln

2,0 g Resomer RG 858 were solved in 38,0 g ethyl acetate (internal phase). 2.0 g Poloxamer 188 (Synperonic F68) were solved in 198,0 g distilled water (phase expressed). The solutions were pumped by means of HPLC pumps (Gynkotec) by a micro mixer (Institut for micro technology, Mainz (IMM), Germany). The micro-channel width amounted to 40 mu M. The phase volume relationship amounted to I: A = 1: 8. The particle size regulation by means of Laserdiffraktometrie (LS 130, Coulter Electronics, the USA) of the freshly dispersed particles resulted in a middle volume diameter D50 of 3,0 mu m, 98% of the particles lay between 0,5 mu m and 11,1 mu M. The middle diameter D50 of the number distribution amounted to 606 Nm.

The completeness of the solvent distance can be shown by the fact that also a Nachtrocknung does not lead no more to a reduction of the particle size. The size of the particles after dispersion with the mixer and after Nachtrocknung are practically identical (fig. 6).

Example 2

Production of particles from hard fat (Witepsol H5)

40.0 g hard fat (Witepsol H5) were melted with 70 DEG C (internal phase). 2.0 g Poloxamer 188 (Synperonic F68) were solved in 198,0 g distilled water (phase expressed). The outside phase was likewise heated up on 70 DEG C. The solutions were pumped by means of HPLC pumps (Gynkotec) by a micro mixer (IMM). The micro-channel width amounted to 40 mu M. The phase volume relationship amounted to I: A = 1: 7. The particle size regulation by means of Laserdiffraktometrie resulted in a middle volume diameter D50 of 2,4 mu m, 98% of the particles lay between 0,6 mu m and 6,9 mu M.

Example 3

Gelatin capsules

1.0 g gel were solved in 39,0 g distilled water with 70 DEG C (phase expressed). 10 ml corn germ oil was warmed up to 70 DEG C (internal phase). The solutions were pumped by means of HPLC pumps by a micro mixer (IMM). The micro-channel width amounted to 40 mu M. The phase volume relationship amounted to I: A = 1: 7. The particle size regulation by means of Laserdiffraktometrie resulted in a middle volume diameter D50 of 2,3 mu m, 98% of the particles lay between 0,4 mu m and 9.1 mu M.

▲ top Example 4

Alginatpartikel, uniformity of the particles

0.5 g Natriumalginat and 0.25 g CaCl2x2H2O were solved in 50,0 ml more aqueous 0.1 m EDTA solution and supplemented with distilled water on 160,0 ml (internal phase). 1.0 g splinter 80 were solved in 175,0 g Propylacetat (phase expressed). As collecting main a solution of acetic anhydride in Propylacetat served. The solutions were pumped by means of HPLC pumps (Gynkotec) by a micro mixer (Institut for micro technology, Mainz, Germany) to the collecting main. The micro-channel width amounted to 40 mu M. The phase volume relationship amounted to I. A = 1: 3. The uniform size of the received micro particles shows the microscopic picture in fig. 7. The micro particles are separated by means of Zentrifugation from the organic phase, taken up in physiological saline solution and removed the remainder solvent by means of CROSS flow filtration.

Example 5

Uniformity of the product after production with micro mixer

PLA Mikropartikel are manufactured after example 1. To the comparison the production with a high-speed agitator Ultra Turrax (Janke and Kunkel, model RW20 DZM) takes place using agitator things S 25 N-10G when 24000 revolutions per minute for 5 minutes. Fig. 8 shows the particle size distributions received with both methods. According to invention manufactured the particles are clearly superior to the particles, which were manufactured by means of Ultra Turrax, regarding the uniformity.

Example 6

Reproductibility of the manufacture method

The prescription of example 1 was six times manufactured and the particle size by means of Laserdiffraktometrie was analyzed. Fig. an overlay of all 6 curves, table 1 shows 9 indicates the most important diameters.

Example 7

Testosteron micro particle

0.2 g Testosteron are solved in 9,8 g acetone (internal phase). 1.4 g Synperonic F68 in 68,6 g distilled water solved (phase expresses). The solutions were pumped by means of HPLC pumps by a micro mixer (IMM). The micro-channel width amounted to 40 mu M. The phase volume relationship amounted to I: A = 1: 7. The particle size regulation by means of Laserdiffraktometrie resulted in a middle volume diameter D50 of 1,5 mu m, 98% of the particles lay between 0,1 mu m and 2.7 mu M.

Example 8

Production of methylenblauhaltigen PLGA micro caps

2.0 g Resomer RG 858 and 0.4 g splinter 80 were solved in 38,0 g ethyl acetate (phase O). 0.025 g blue were solved in 9,975 g distilled water (phase W1). The solutions were pumped by means of HPLC pumps (Gynkotec) by a micro mixer (Institut for micro technology, Mainz, Germany). The micro-channel width amounted to 25 mu M. The phase volume relationship amounted to W1: O = 1 : 4.
The developed W/O Emulsion was led into a second micro mixer with micro-channel width by 40 mu m. As the second phase an aqueous 4%ige Poloxamer 188 (Synperonic F68) was in addition-given solution (phase W2). The phase volume relationship amounted to (W 1/O): W2 = 1,5: 8,5.
The resulting caps showed a middle volume diameter of D50 = 1.059 mu m, 98% of the micro caps lay between 0,13 mu m and 5.14 mu M.

Example 9

Micro particles were manufactured similar to example 1. Additionally 0.2 g Ethinylestradiol were solved in the organic phase.

Example 10

Micro particles were manufactured similar to example 1. Additionally 0.2 g Estradiol were solved in the organic phase.

Example 11

Micro particles were manufactured similar to example 1. Additionally 0.2 g Testosteron were solved in the organic phase.

Example 12

▲ top

Micro particles were manufactured similar to example 1. Additionally 0.2 g Gestoden were solved in the organic phase.

Example 13

Micro particles were manufactured similar to example 1. Additionally 0.2 g Levonorgestrel were solved in the organic phase.